This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 SYNOPSIS

Title of Study:	Study to Evaluate the Effect of the Coadministration of SCH 497079 (a Histamine 3 [H3] Receptor Antagonist) Plus Desloratadine on Nasal Congestion in Subjects With Seasonal Allergic Rhinitis Who Have Been Exposed to Pollen in the Vienna Challenge Chamber (VCC) (Protocol No. P02561, Abbreviated Study Report)	
Investigator(s):	[redacted]	
Study Center(s):	[redacted]	Austria
Publication(s):	None	
Studied Period:	13 OCT 2004 to 17 JAN 2005	**Clinical Phase: 2**

Objective(s)

Primary Objective(s): The primary objective of this study was to evaluate the effect on nasal congestion of a maximally tolerated dose (identified in Phase 1 studies) of SCH 497079 (H3), when taken in combination with desloratadine (DL) 5 mg, in subjects with seasonal allergic rhinitis (SAR) who had been exposed to pollen in the Vienna Challenge Chamber (VCC). This objective was accomplished by comparison of the effect on nasal congestion, over a 7.5-hour observation period, of the coadministration of H3 100 mg and DL 5 mg with that of DL 5 mg taken alone.

Secondary Objective(s): Key secondary objectives included calculation of the estimates of the following treatment differences over the 7.5-hour observation period and at each time point:

- Comparison of the effect on nasal congestion of the coadministration of H3 20 mg and DL 5 mg with that of DL 5 mg taken alone;
- Comparison of the effect on nasal congestion of DL 5 mg taken in combination with each of two dose levels of H3 (100 and 20 mg) vs concurrent administration of DL 5 mg plus pseudoephedrine (PSE) 240 mg;
- Objective measurement of nasal airflow by subject-assessed measurement of peak nasal inspiratory flow (PNIF) using a Youlton Nasal Peak Inspiratory Flow Meter device;
- Objective measurements by means of anterior rhinomanometry of nasal airflow through the combination of left plus right nostrils;
- Evaluation of the safety profiles among the five treatments of postdose vital signs and adverse events compared with predose evaluations; and
- Single-dose plasma H3, DL, 3-OH DL, and PSE concentrations and pharmacokinetic parameters were to be listed and summarized using means and percent coefficients of variation (CV%). In addition, an association between plasma concentrations and observed decongestant activity was to be explored if the data allowed.

Methodology: This was a randomized, double-blind, placebo-controlled, quadruple-dummy, five-way crossover study (with a minimum of a 10-day washout between crossovers) in subjects with documented summer seasonal (grass) allergies. The study was conducted at a single center in Austria. The comparisons were H3 100 mg plus DL, H3 20 mg plus DL, DL plus PSE 240 mg, DL alone, and placebo in subjects with SAR. The study was conducted in conformance with Good Clinical Practices. A 20-mg dose of H3 plus DL was chosen to determine whether a dose response could be detected in the chamber model. The primary efficacy variable, subjective evaluation of nasal congestion, was to be recorded by subjects at 15-minute intervals by means of a computer-based online diary. Six additional signs/symptoms (rhinorrhea, sneezing, nasal itching, eye itching/burning, eye tearing/watering, and itching of ears/palate) were also to be recorded. Secondary objective assessments of effects on nasal congestion/nasal airflow were to include subject-assessed peak nasal inspiratory flow, measured at 30-minute intervals, and evaluation of airflow through the left and right nostrils by means of anterior rhinomanometry instrumentation, also carried out at 30-minute intervals.

Two terminal blood samples (5 mL each) were to be collected from each subject at each treatment visit at 7.5 hours postdose to demonstrate exposure of H3, DL, 3-OH DL, and PSE. Plasma H3, DL, 3-OH DL, and PSE concentrations were to be listed and summarized using means and percent coefficients of variation (CV). In addition, an association between plasma concentrations and observed decongestant activity was to be explored if the data allowed.

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Number of Subjects: Sixty-nine subjects were randomized to treatment; 64 subjects completed all five treatment phases.

Diagnosis and Criteria for Inclusion: Subjects with a history of SAR who met the following criteria were enrolled in the study.

Key Inclusion Criteria:

- Subjects were between 18 and 45 years of age, of any race, with at least a 2-year history of summer SAR;
- Positive skin test to confirm hypersensitivity to *Dactylis glomerata* grass allergen extract (which is cross-reactive with the pollen mixture used in the chamber) unless a positive test was obtained within the previous 12 months. IgE-mediated hypersensitivity must have been documented by a positive response to the skin prick test with wheal diameter ≥3 mm larger than diluent control;
- Minimum symptom scores on a scale of 0–3 at some point during each of the 120-minute screening period challenge sessions as follows:
  - Nasal Congestion Score of at least 2 (moderate);
  - Total Nasal Symptom Score of at least 6;
  - Total Non-nasal Symptom Score of at least 2; and
- Freedom from any clinically significant disease (other than SAR) that would interfere with the study evaluations or compromise the subject's safety.

Key Exclusion Criteria:

- Upper or lower respiratory tract infection within 4 weeks before Screening or at any time during the study;
- Known potential for hypersensitivity, allergy, or idiosyncratic reaction to any of the study drugs or to the excipients;
- Dependence on nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids;
- Nasal structural abnormalities, including large nasal polyps or marked septal deviation, that significantly interfered with nasal airflow; and
- Rhinitis medicamentosa.

Test Product, Dose, Mode of Administration, Batch No(s): Coadministered combination of H3 100-mg capsule and DL 5-mg QD/PO tablet; coadministered combination of H3 20 mg (two 10-mg capsules) and DL 5-mg QD/PO tablet. The batch numbers for the H3 10- and 100-mg capsules were [redacted] respectively. The batch number for the DL 5-mg tablet was [redacted]

Duration of Treatment: After a screening phase of 1 to 28 days, subjects received one dose of treatment at each of five treatment visits. There was at least a 10-day washout period between each treatment visit.

Reference Therapy, Dose, Mode of Administration, Batch No(s): DL 5-mg tablet (Batch No. [redacted] and matching placebo (Batch No. [redacted] PSE 240-mg sustained-release tablet (Batch No. [redacted] and matching placebo (Batch No. [redacted] placebo capsules matching H3 10- and 100-mg capsules (Batch Nos. [redacted] respectively).

Criteria for Evaluation: Improvement in symptom scores and safety assessments.

Primary Efficacy Endpoint/Primary Treatment Comparison: The primary efficacy variable was the subjectively evaluated nasal decongestant effect, expressed as an average change from Baseline in the diary-based symptom of nasal congestion, over the 7.5-hour observation period. The primary comparison for this variable was H3 100 mg plus DL 5 mg taken in combination vs DL 5 mg alone.

Key Secondary Treatment Comparisons: The key secondary treatment comparisons with respect to the primary efficacy variable (average change from Baseline in nasal congestion over the 7.5-hour observation

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period) were

- H3 20 mg plus DL 5 mg taken in combination vs DL 5 mg alone
- H3 100 mg plus DL 5 mg taken in combination vs DL 5 mg plus PSE taken in combination
- H3 20 mg plus DL 5 mg taken in combination vs DL 5 mg plus PSE taken in combination
- DL 5 mg plus PSE taken in combination vs placebo
- DL 5 mg plus PSE taken in combination vs DL 5 mg alone
- DL 5 mg vs placebo

Secondary Efficacy Endpoints: Change from Baseline in nasal congestion at each time point.

Other Secondary Comparisons:

- Average change from Baseline in total and individual symptom scores over the study period and at each time point;
- Onset of action of effect on total symptoms and of nasal decongestive effect, defined as the first time point at which a consistent statistically significant (P ≤0.05) reduction in total symptom score or reduction of nasal congestion, was achieved (active vs placebo) and maintained over succeeding time points relative to predose baseline symptom scores;
- Average change from Baseline in PNIF over the study period and at each time point; and
- Average change from Baseline in total of right plus left nostril airway flow as measured by anterior rhinomanometry over the study period and at each time point.

All pairwise treatment comparisons were to be performed for all efficacy endpoints.

Safety evaluations consisted of postdose adverse event evaluation and vital signs compared with predose observations and values. Postdose blood pressure and pulse were to be collected every 2 hours at each treatment visit and at the final time point. Additional collection of blood pressure and pulse data was to be performed only at the investigator's decision.

Statistical Methods: For primary and secondary variables, pairwise comparisons were to be made using linear contrasts of the treatment means obtained from an analysis of variance (ANOVA) model that extracted sources of variation due to treatment, subject, and phase. No adjustment to the significance level was necessary because a single primary comparison was stated. All analyses and summaries were to be based on all randomized subjects (intent-to-treat principle). Using a two-sided test, a sample size of approximately 50 patients for this crossover design ensured 80% power to detect a difference of at least 0.30 points in change from Baseline in nasal congestion score between two treatment groups, at an alpha = 0.05 significance level, assuming a pooled standard deviation of 0.53 on change from Baseline in nasal congestion score.

SUMMARY - CONCLUSIONS:

RESULTS:

Efficacy: The average change in postbaseline nasal congestion score in all randomized subjects was -28% for H3 100 mg + DL 5 mg compared with -25% for H3 20 mg + DL 5 mg, -37% for PSE 240 mg + DL 5 mg, -21% for DL 5 mg, and -9% for placebo. H3 100 mg + DL 5 mg did not differentiate from DL 5 mg alone in average postbaseline nasal congestion score. In addition, the effect of H3 100 mg + DL 5 mg on nasal congestion relative to that of DL alone was <70% of that produced by PSE 240 mg + DL 5 mg. Similar results were obtained for all randomized subjects who completed all five treatment phases.

Pharmacokinetics: Mean plasma H3 concentrations increased with increasing doses (100 vs 20 mg). Mean plasma concentrations for DL and 3-OH DL were similar when DL 5 mg was given alone, coadministered with H3, or coadministered with PSE.

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Mean (CV%) Plasma Concentrations of H3, DL, 3-OH DL, and PSE at 7.5 Hours Postdose in Subjects With SAR

Treatment	Active Treatment	n	Mean (CV%) Plasma Concentration (ng/mL)			
			3-OH DL	DL	H3	PSE
1	H3 100 mg/DL 5 mg	67	1.17 (30)	1.69 (36)	456 (30)	–
2	H3 20 mg/DL 5 mg	64	1.19 (27)	1.63 (34)	95.0 (33)	–
3	DL 5 mg/PSE 240 mg	67	1.22 (27)	1.62 (35)	–	324 (27)
4	DL 5 mg	66	1.18 (30)	1.68 (37)	–	–

Safety: Five treatment-emergent adverse events were reported during the study. Two placebo-treated subjects and one subject administered PSE 240 mg + DL 5 mg reported upper respiratory tract infections (URIs). One subject administered H3 20 mg + DL 5 mg reported epistaxis; one subject treated with H3 100 mg + DL 5 mg reported abdominal pain. All adverse events were mild to moderate and resolved spontaneously. Only abdominal pain was considered by the investigator to be possibly related to treatment. There were no serious adverse events. Four subjects discontinued from study medication because of adverse events: three subjects because of URIs and one subject because of abdominal pain. No clinically relevant changes were noted in vital signs.

CONCLUSIONS:

- H3 100 mg + DL 5 mg did not differentiate from DL 5 mg in average postbaseline nasal congestion score.
- Mean plasma H3 concentrations increased with increasing doses (100 vs 20 mg). Mean plasma concentrations for DL and 3-OH DL were similar when DL 5 mg was given alone, coadministered with H3, or coadministered with PSE.
- All treatments administered were safe and well tolerated. There were no notable treatment differences in the incidence of adverse events or in vital signs.
- An abbreviated study report was prepared because of the lack of evidence of efficacy in this indication.

Date of the Report: 31 MAR 2006